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SAMPLE-BASED REPORTING OF OFFICIAL NATIONAL CONTROL OF VETERINARY DRUG RESIDUES

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Abstract
Data collection is an essential prerequisite for assessing compliance of chemical residues in food and for risk assessment. The present system for collecting aggregated data of residues of veterinary medicinal products and other substances in animals and animal products has limitations for risk assessment as well as risk management.
The European Food Safety Authority has been assigned with the task to set up a system for data collection based on individual analytical results. A pilot project has been launched with participants from eleven Member States for parallel reporting of monitoring results from 2015 in aggregated form as well as individual analytical results using a standardised data model. The challenges that face the pilot participants include provisions for categorised sample information, specific method performance data, result evaluation and follow-up actions.
Experience gained through the reporting of monitoring data from Denmark will be presented.

Introduction

Presently, all Member States (MSs) of the European Union (EU) are obliged to report their monitoring results for veterinary drug residues and other substances in live animals and animal products according to Council Directive 96/23/EC (EC 1996) through the Sanco Residue web based application for monitoring plans and results (EC 2009).

This allows MSs to report on a yearly basis results from samples analysed for the official control according to the directive.

However, samples are grouped in very broad categories according to the directive: bovine, pigs, horses, sheep/goats, poultry, aquaculture, milk, eggs, rabbit, farmed game, wild game and honey. Sampling points can be reported as 'farm' or 'slaugterhouse' where relevant and sampling strategy can be reported as 'target' or 'suspect'. The two remaining sampling groups are 'import' and 'others'.

Also residue substances are grouped in broad categories as defined in the directive (six groups of substances having anabolic effect and unauthorized substances (stilbenes and stilbene derivatives; antithyroid agents; steroids; resorcylic acid lactones; beta-agonists; compounds included in Annex IV to Council Regulation 2377/90), seven groups of veterinary drugs (antibacterial substances; anthelmintics; anticoccidials; carbamates and pyrethroids; sedatives; non-steroidal anti-inflammatory drugs; other pharmacologically active substances) and six groups of contaminants and other substances (organochlorine compounds including PCBs; organophosphorus compounds; chemical elements; mycotoxins; dyes; others)). Individual substances are only reported when non-compliant results have been found, and no concentration levels are reported.

The European Food Safety Authority (EFSA) has since the 2008 data collection assisted the European Commission with compiling and publishing a technical report on the occurrence of residues of veterinary drugs and other substances monitored according to the directive (EFSA 2010a).

Due to the limited level of details in reporting positive findings, the reports have been focusing on risk handling aspects of the monitoring, *i.e.* the number of samples in comparison to the National Residue Control Plans that MSs also report to the same web based application, and the frequencies of non-compliant results and/or samples for the different broad sampling groups.

A number of limitations due to the reporting practices have been pointed out in the EFSA reports: The information on sample identification, sample matrix and the corresponding results is not available and thus it is impossible to perform a more elaborate statistical analysis at the matrix level (meat, liver, blood *etc.)* and to identify the samples non-compliant for more substances (multi-residues samples). Neither is information on the occurrence of veterinary medicinal product residues (VMPR) at levels below MRLs available. (EFSA 2010b, EFSA 2015a).

Collection of sample-based data would allow a more elaborate data analysis and would enable the Commission, MSs and EFSA to answer additional questions in relation to VMPR monitoring results.

Pesticides have also been reported to the Commission in aggregated form, but in 2009 EFSA set up a pilot project for sample-based reporting of pesticide residues using a preliminary version of what is now known as the EFSA Standard Sample

Description. A revised Guideline was published in late 2009 aimed at the reporting of chemical contaminants and pesticide residues (EFSA 2010c).

In 2013, EFSA published the Guidance on Standard Sample Description version 2.0 (SSD2) (EFSA 2013a) with the purpose of unifying all data collections in a single data reporting model and to a common list of harmonised controlled terminologies. The SSD2 is designed to harmonise the transmission of data from data providers to EFSA covering several data collection domains, *i.e.* food additive occurrence data, chemical contaminants occurrence data, pesticide residues, and residues of veterinary medicinal products as well as zoonoses, antimicrobial resistance and food-borne outbreak data.

SSD2 is complemented by the Guidance on Data Exchange version 2 (EFSA 2014), which supports SSD2 with harmonised technical specifications about transmission requirements, metadata and general business rules definition.

The National Food Institute at the Technical University of Denmark has been involved in several EFSA pilot projects on data collection using SSD for structuring and transmission of sample-based results from the official national control and monitoring programs under the auspices of the Danish Veterinary and Food Administration (DVFA), who is the national authority for risk management of food. Presently the institute, in cooperation with DVFA, is engaged in the EFSA pilot project on the implementation of SSD2 for reporting residues of veterinary medicinal products for the 2015 monitoring programmes according to Council Directive 96/23/EC (EFSA 2015b).

Materials and Methods

Laboratories

Samples for the official control of residues of veterinary medicinal products in Denmark are almost exclusively analysed at the DVFA control laboratory in Ringsted, Denmark. A few types of analysis are performed at The National Food Institute in Mørkhøj, Denmark, either where the relevant methods have not yet been implemented at the control laboratory or as part of a technical assistance. In addition, a few agreements exist for confirmatory analysis at laboratories outside Denmark.

Analyses for some non-drug substances included in the Directive 96/23 monitoring are performed at the DVFA laboratory in Aarhus, Denmark.

In all cases, the DVFA laboratories are responsible for both sampling and result registration. Consequently, information on sampling and analysis is collected in the same laboratory information system (LIMS) (LabVantage® LIMS 6.0). The LIMS is integrated in the DVFA data warehouse (DW) (Microsoft SQL Server®). The DVFA DW also includes information from other administrative systems such as registers of controlled establishments and inspections databases.

Data extraction

During the previous SSD pilot projects on data transformation and transmission to EFSA, an automated, dedicated extraction procedure has been set up to extract specific data elements from the DVFA DW. Based on a list of programme identifiers these data are transmitted to an Oracle database at the National Food Institute when relevant.

In order to cater for the requirements of the VMPR domain, the previously identified data elements have been expanded with a few elements, including decision limit (CCα) and detection capability (CCβ) (EC 2002).

The extracted data include elements for transformation to the SSD data model as well as supplementary elements for *e.g.* validation of registrations.

Transformation

The core functionality has been built around a configurable transformation system based on the Microsoft Excel® version of the SSD2 data definitions (EFSA 2013b). These tables are compiled by a suit of SAS procedures (SAS® Enterprise Guide 6.1; SAS® 9.4) into a program that transforms the extract from the DVFA DW to a SSD2 compatible SAS dataset.

The process includes several types of transformation as exemplified in Table 1. The different transformation types are described in Table 2.

The lookup facility is used both for simple translation of national terms (*e.g.* country of origin of the sample) to SSD2 terms/codes but also to facilitate reporting of certain types of information that is not readily available from the data warehouse (*e.g.* adding information on method type (screening/confirmation) and method principle (ELISA/LC-MSMS *etc.*)).

Some types of information needs further processing, *e.g*. result evaluations, follow-up actions and conclusions or handling of analytical substances (parameter codes) for complex residue definitions (*e.g.* albendazole: “Sum of albendazole sulphoxide, albendazole sulphone, and albendazole 2-amino sulphone, expressed as albendazole”).

Table 1. Example of SSD data definitions and associated transformation columns

SSD2 Element code	SSD2 Element label	Type	DTU	LIMS	Catalogue	Lookup column
sampCountry	Country of sampling	String(2)	Constant	DK		
sampID	Sample ID	String(100)	Copy	Proeve_ID		
sampArea	Area of sampling	String(5)	[a)]			
sampY	Year of sampling	Integer	Function	year(Dato_udtaget)		
origCountry	Country of origin	String(2)	Lookup	Oprindelse_land	EFSAcountry	countryCode
anMethRefId	Analytical method	String(50)	Copy	Testmetode_ID		
anMethType	Analytical method type	String(5)	Lookup	Testmetode_ID	EFSAmethod	ANLYTYP
anMethCode	Analytical method code	String(5)	Lookup	Testmetode_ID	EFSAmethod	ANLYMD

[a)] empty

Table 2. Transformation of data from the data warehouse of the Danish Veterinary and Food Administration to the EFSA Standard Sample Description 2.0

Transformation type	Explanation
Constant	Value in column LIMS is inserted into the SSD2 Element
Copy	Value of the LIMS element named in column LIMS is inserted into the SSD2 Element
<empty>	Element not included in SSD2 file
Function	Function output of value of the LIMS element named in column LIMS is inserted into the SSD2 Element
Lookup	Value of LIMS element in column LIMS is used as a key for lookup in the translation catalogue named in column Catalogue.

Data validation

Technical validations according to relevant business rules are performed by SAS procedures. Scientific and administrative reviews are performed by specialists at the National Food Institute and/or DVFA laboratories.

XML formatting

The final validated SAS dataset is written as a XML formatted text file (Extensible Markup Language (W3C 2004)) using a dedicated SAS procedure that minimizes the file size by excluding all empty elements.

Transmission

The XML file is manually uploaded to the designated EFSA web page (Data Collection Framework). Following the upload an automatic technical validation will be performed by EFSA before the file is accepted for further processing at EFSA.

Results and Discussion

Challenges in VMPR reporting

The fact that the monitoring activities for official food control in Denmark has been centralised to one administration (the Danish Veterinary and Food Administration) and that the relevant information exists in a centralised data warehouse has simplified the implementation of the system for reporting of VMPR since the major part of the necessary infrastructure already was in place.

Legal limits and evaluations. However, each chemical domain has its special requirements for information; the VMPR domain has several requirements in common with the pesticide domain. In both domains a legal requirement for an annual report from a central European authority exists, and these reports must include information on residues in relation to legally accepted residue levels.

Consequently there is a need for a detailed reporting of the legal limit that has been the basis for the subsequent evaluation of the result, the administrative actions that have followed for samples evaluated as non-compliant, and also the conclusions drawn from follow-up investigations of non-compliant or suspect samples.

This information is not in all cases directly available in machine readable form from the data warehouse and may need expert judgement from trained personnel. For this reason all results above the reported limit values and results from suspect samples are extracted to an Excel file and circulated to the responsible person(s) at DVFA who will then correct/supplement information on evaluation, actions taken and conclusions of follow-up investigations. Subsequently this information will be loaded back into the SSD2 structured file before reporting to EFSA.

Multi methods. In many cases the analytical programmes are implemented using multi methods. In most cases only results for the detected substances are reported for these methods or information indicating that the method has been applied without detections. The prescriptions of SSD2 require that an individual result is reported for each substance included in the method scope. This is also the case for screening methods. Consequently the report lines must be expanded, using information from a method/substance catalogue that is setup in corporation with the laboratory.

For detected substances analytical limits (limits of detection (LOD), quantification (LOQ) and decision (CCα) and detection capability (CCβ)) can be reported in LIMS together the measured result. For substances not reported – or only implicitly reported by the reported method, information on analytical limits must be supplied from the method/substance catalogue. The situation is very much the same in the pesticide domain, and experience and implementations from that domain have been drawn upon for the reporting of VMPRs.

Screening methods. Screening methods are applied and reported for several substance groups. In case of positive screening results a confirmatory quantitative analysis must be performed subsequently and reported in the LIMS. However, double reporting cannot be transmitted in the SSD2 data model, so whenever results from a confirmatory method has been reported for a sample together with a screening result for the same substance, the screening result must be deleted before reporting in the SSD2 data model. Such functionality has already been implemented to cater for the equivalent situation in the additives domain.

Future challenges

The EFSA SSD2 data model for VMPRs has been designed to fulfil the present requirements for reporting according to Directive 96/23. However, the data model will be able to accept more detailed information on the analyses performed, should this be required. Such detailed reporting could be relevant for both risk assessment and risk management, adding value for stakeholders in this field.

Matrix analysed. Today the requirements for detailed reporting of the type of matrix analysed is very limited in relation to result reporting, although the National Residue Control Plans, required by the Directive, often shows more details. The SSD2 data model will allow for a detailed description of the samples taken, both in terms of describing the animal (sex, age *etc.*) as well as the type of matrix analysed (muscle, urine *etc.*). Traditionally, in Denmark, details on these matters have only been reported in a textual file on follow-up measures. A change from reporting 'Bovine' and details on *e.g.* sex and age in free text (which is not in good keeping with the SSD2 data model) to a categorised form via the LIMS product catalogue would be a limited effort for future reporting, thus making this information available for assessments at EFSA or the EU Reference Laboratories.

Method capabilities. Today's possibilities of using advanced instrumental analyses like liquid chromatography coupled with mass spectrometric detection have lead the DVFA laboratories to abandon the traditional microbiological and some of the biochemical screening methods, replacing these with chemical instrumental analyses. These techniques may still be used as screening methods, meaning that analytical efforts are concentrated on samples with residues close to or above the legal limits. Utilising the full potential of these methods to determine residues well below the legal limits would certainly provide more information to assess the impact of residues in products of animal products, but might inflict an increased cost due to a higher rate of necessary quantifications and maybe initially also additional validation.

Conclusions

A system for transformation and transmission of sample based reporting of individual analytical results using a standardised data model has been designed and partially implemented. The existing system for transformation of analytical results from chemical occurrences and pesticide residues is foreseen to be able to cope with the reporting of results from monitoring of residues of veterinary medicinal products with only minor adjustments. Apart from a necessary updating of catalogues to include relevant sample descriptions, methods and substances, a major challenge will be the handling of legal limits and evaluations which might require some manual interaction.

The data model will allow a more detailed description of samples and results than the present reporting of aggregated data, which will improve the usefulness of the data collection for risk management and risk assessment.

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